REMARKS/ARGUMENTS

The amendments to the claims are fully supported by the specification and claims as originally filed and do not constitute new matter. Applicants believe that the current amendments place all claims in *prima facie* condition for allowance or, at least, in a better form for consideration on appeal. Accordingly, the consideration and entry of the present amendment after final rejection is respectfully requested.

Prior to the present amendment, Claims 28-35, 38-40 were pending in this application. With this amendment, Claims 28-32 have been amended to recite an "isolated native sequence polypeptide." Support for the term "native sequence" can be found in the specification at, for example, page 301, lines 9-21. A "native sequence PRO polypeptide" comprises a polypeptide having the same amino acid sequence as the corresponding PRO polypeptide derived from nature. Such native sequence PRO polypeptides can be isolated from nature or can be produced by recombinant or synthetic means. The term "native sequence PRO polypeptide" specifically encompasses "naturally-occurring truncated or secreted forms of the specific PRO polypeptide ... naturally occurring variant forms ... and naturally occurring allelic variants of the polypeptide."

Claims 28-32 have also been amended to recite polypeptides comprising a polypeptide sequence having at least 80-99% amino acid sequence identity to the amino acid sequence of the polypeptide of SEQ ID NO:397, with or without its signal peptide sequence, or the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 203480. Support for polypeptides comprising polypeptide variants is found in the specification at, for example, page 283, lines 2-27.

Claims 28-35 and 38-40 are pending after entry of the instant amendment. Applicants expressly reserve the right to pursue any canceled matter in subsequent continuation, divisional or continuation-in-part applications.

Applicants note and appreciate the withdrawal of the earlier objections and rejections under 35 U.S.C. §112, second paragraph, and 35 U.S.C. §102. The remaining rejections under 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph, are addressed below.

In addition, Applicants request the PTO to take note of the Revocation and Power of Attorney and Change of Address filed on February 28, 2003 and kindly direct all future correspondence to the address indicated, *i.e.*, to:

CUSTOMER NO. 35489
Ginger R. Dreger
Heller Ehrman LLP
275 Middlefield Road
Menlo Park, California 94025
Telephone: (650) 324-7000
Facsimile: (650) 324-0638

I. Information Disclosure Statement

The Examiner states that the Information Disclosure Statement filed January 16, 2005 fails to comply with 37 C.F.R. 1.98(a)(2), which requires a legible copy of each cited foreign patent document, each non-patent literature publication or that portion which caused it to be listed, and all other information or that portion which caused it to be listed. The Examiner states that these references have been considered to the extent possible, but that allegedly no direct comparisons between the listed sequences and those claimed have been provided, and thus they will not be printed on the face of the patent issuing from this application.

Applicants respectfully point out that the Information Disclosure Statement filed January 18, 2005 (not January 16, 2004, as stated in the Office Action) was filed in part for the purpose of correcting the format of the original IDS by listing each reference of the BLAST searches separately. See the Response to Office Action filed January 18, 2005. The IDS filed January 18, 2005 included authors/inventors, relevant accession numbers and publication dates for each individual sequence found in the two previously submitted BLAST searches. References 1-10 are the database entries for the polypeptide sequences found in the BLASTP 2.2.1 search, while references 11-23 are the database entries for the nucleic acid sequences found in the BLASTN 2.2.1 search. These references are intended to replace or supplement the polypeptide BLASTP 2.2.1 and nucleic acid BLASTN 2.2.1 search listings. The actual sequence alignments between the listed sequences and those claimed have already been provided in the BLASTP 2.2.1 and BLASTN 2.2.1. The IDS filed January 18, 2005 simply added authors/inventors, relevant accession numbers and publication dates for each of these sequences. Applicants respectfully request that the information listed be considered by the Examiner in its entirety and made of record in the instant application.

II. Claim Rejections Under 35 U.S.C. § 101 and 35 U.S.C. § 112, First Paragraph

Claims 28-35 and 38-40 remain rejected under 35 U.S.C. § 101 allegedly "because the claimed invention is not supported by either a specific and/or substantial asserted utility or a well established utility." In particular, the Examiner asserts that "the specification does not identify a single 'reasonable use' for the claimed polypeptides of the instant invention. In other words, the claimed functional use of DNA for detecting colon tumors is not equivalent to identifying a use for the claimed polypeptides." (Page 3 of the instant Office Action).

Claims 28-35 and 38-40 also remain rejected under 35 U.S.C. § 112, first paragraph, allegedly "since the claimed invention is not supported by either a specific and/or substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention." (Page 10 of the instant Office Action).

Applicants respectfully disagree and traverse the rejections. Applicants submit that Claims 28-35 and 38-40 have patentable utility and enablement for the reasons discussed below.

Utility – Legal Standard

According to 35 U.S.C. § 101:

> Whoever invents or discovers any new and *useful* process, machine, manufacture, or composition of matter, or any new and *useful* improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title. (Emphasis added.)

In interpreting the utility requirement, in *Brenner v. Manson*[1] the Supreme Court held that the quid pro quo contemplated by the U.S. Constitution between the public interest and the interest of the inventors required that a patent applicant disclose a "substantial utility" for his or her invention, i.e. a utility "where specific benefit exists in currently available form."[2] The Court concluded that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion. A patent system must be related to the world of commerce rather than the realm of philosophy."[3]

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[1] *Brenner v. Manson,* 383 U.S. 519, 148 U.S.P.Q. (BNA) 689 (1966).

[2] *Id.* at 534, 148 U.S.P.Q. (BNA) at 695.

[3] *Id.* at 536, 148 U.S.P.Q. (BNA) at 696.

Later, in *Nelson v. Bowler*[4] the C.C.P.A. acknowledged that tests evidencing pharmacological activity of a compound may establish practical utility, even though they may not establish a specific therapeutic use. The court held that "since it is crucial to provide researchers with an incentive to disclose pharmaceutical activities in as many compounds as possible, we conclude adequate proof of any such activity constitutes a showing of practical utility."[5]

In *Cross v. Iizuka*[6] the C.A.F.C. reaffirmed *Nelson*, and added that *in vitro* results might be sufficient to support practical utility, explaining that "*in vitro* testing, in general, is relatively less complex, less time consuming, and less expensive than *in vivo* testing. Moreover, *in vitro* results with the particular pharmacological activity are generally predictive of *in vivo* test results, i.e. there is a reasonable correlation there between."[7] The court perceived "No insurmountable difficulty" in finding that, under appropriate circumstances, "in vitro testing, may establish a practical utility."[8]

The case law has also clearly established that applicants' statements of utility are usually sufficient, unless such statement of utility is unbelievable on its face. [9] The PTO has the initial burden that applicants' claims of usefulness are not believable on their face.[10] In general, an Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. §101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope."[11], [12]

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[4] *Nelson v. Bowler*, 626 F.2d 853, 206 U.S.P.Q. (BNA) 881 (C.C.P.A. 1980).

[5] *Id.* at 856, 206 U.S.P.Q. (BNA) at 883.

[6] *Cross v. Iizuka*, 753 F.2d 1047, 224 U.S.P.Q. (BNA) 739 (Fed. Cir. 1985).

[7] *Id.* at 1050, 224 U.S.P.Q. (BNA) at 747.

[8] *Id.*

[9] *In re Gazave*, 379 F.2d 973, 154 U.S.P.Q. (BNA) 92 (C.C.P.A. 1967).

[10] *Ibid.*

[11] *In re Langer*, 503 F.2d 1380,1391, 183 U.S.P.Q. (BNA) 288, 297 (C.C.P.A. 1974).

[12] *See also In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (C.C.P.A. 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (C.C.P.A. 1977).

Compliance with 35 U.S.C. §101 is a question of fact.[13] The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration.[14] Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Only after the Examiner made a proper *prima facie* showing of lack of utility, does the burden of rebuttal shift to the applicant. The issue will then be decided on the totality of evidence.

The well established case law is clearly reflected in the Utility Examination Guidelines ("Utility Guidelines")[15], which acknowledge that an invention complies with the utility requirement of 35 U.S.C. §101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility." Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic without also identifying the conditions that are to be diagnosed.

In explaining the "substantial utility" standard, M.P.E.P. §2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a "'substantial'" utility.'"[16] Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement,[17] gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill

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[13] *Raytheon v. Roper*, 724 F.2d 951, 956, 220 U.S.P.Q. (BNA) 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984).

[14] *In re Oetiker*, 977 F.2d 1443, 1445, 24 U.S.P.Q.2d (BNA) 1443, 1444 (Fed. Cir. 1992).

[15] 66 Fed. Reg. 1092 (2001).

[16] M.P.E.P. §2107.01.

[17] M.P.E.P. §2107 II (B)(1).

in the art, do not impose a rejection based on lack of utility."

Proper Application of the Legal Standard

The specification provides sufficient disclosure to establish a specific, substantial and credible utility for the PRO1788 polypeptide.

The Examiner asserts:

> the specification provides data showing a very small increase in **DNA** copy number of approximately **2-fold** in a few tumor samples for PRO1788. The specification fails to provide any evidence on whether or not the PRO1788 **mRNA** or **polypeptide** levels are also increased in these tumor samples. Because the instant claims are directed to **PRO1788 polypeptide**, it is imperative to find evidence in the relevant scientific art as to whether or not a small increase in DNA copy number would be considered by the skilled artisan to be predictive of increases in mRNA and subsequent polypeptide levels. (Pages 6-7 of the instant Office Action).

The Examiner incorrectly characterizes the data provided in the specification as "showing a very small increase in **DNA** copy number of approximately **2-fold** in a few tumor samples for PRO1788" (page 6 of the instant Office Action). Applicants respectfully point out that nucleic acids encoding PRO1788 had ΔCt value of > 1.0, which is a **more than 2-fold increase**, for **eight** different primary colon tumors: CT1, CT3, CT4, CT8, CT9, CT10, CT12, and CT14. The actual amount of increase ranges from 2.12-fold for CT1, to **6-fold** for CT14. Thus the specification clearly shows a significant increase in DNA copy number, in a wide range of colon tumor samples.

In addition, Example 143 discloses that: "Amplification is associated with overexpression of the gene product, indicating that the polypeptides are useful targets for therapeutic intervention in certain cancers such as colon, lung, breast and other cancers." Applicants have further submitted the Declaration by Audrey Goddard, Ph.D. in the Response filed January 18, 2005, which clearly establishes that the TaqMan realtime PCR method described in Example 143 has gained wide recognition for its versatility, sensitivity and accuracy and is in extensive use for the study of gene amplification. Dr. Goddard in her Declaration confirms that an at least 2-fold increase in gene copy number in a tumor tissue sample relative to a normal (*i.e.,* non-tumor) is significant and useful. The Goddard Declaration further confirms that based on the gene amplification results set forth in Table 8, one of ordinary skill would find it credible that an at least 2-fold increase in gene copy number (as seen with PRO1788) would indicate that the gene

is a diagnostic marker of human lung cancer.

In their Response filed January 18, 2005, Applicants also submitted the Declaration by Avi Ashkenazi, Ph.D., an expert in the field of cancer biology and a Director of the Molecular Oncology Department at Genentech, Inc., the assignee of the present application. In his Declaration, Dr. Ashkenazi states, "If gene amplification results in over-expression of the mRNA and corresponding gene product, then it identifies that gene product as a promising target for cancer therapy, for example by the therapeutic antibody approach."

Accordingly, Applicants respectfully submit that Applicants' assertion that the asserted utility for the PRO1788 polypeptide, for example in the detection of lung cancer, is substantial.

The Examiner contends that the declarations of Dr. Goddard, Dr. Ashkenazi and Dr. Polakis filed under 37 CFR 1.132, all filed January 18, 2005, are insufficient to overcome the rejection of claims 28-35 and 38-40, based upon 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph. (See page 3 of the instant Office Action).

Applicants respectfully disagree and traverse the rejection.

First of all, Applicants have previously submitted references by Ornoft *et al.,* Hyman *et al.,* and Pollack *et al.* As previously stated in the Applicants' response filed on January 18, 2005, these articles collectively teach that in general, gene amplification increases mRNA expression.

Applicants have submitted Dr. Goddard's Declaration to show that the TaqMan real-time PCR method described in Example 143 has gained wide recognition for its versatility, sensitivity and accuracy, and is in extensive use for the study of gene amplification. The facts disclosed in the Declaration also confirm that based upon the gene amplification results, one of ordinary skill would find it credible that PRO1788 is a diagnostic marker of lung cancer. Applicants emphasize that the opinions expressed in the Goddard Declaration are all based on factual findings. Thus, Dr. Goddard explains that the TaqMan PCR assay is based on the principle that successful PCR yields a fluorescent signal due to Taq DNA polymerase-mediated exonuclease digestion of a fluorescently labeled oligonucleotide that is homologous to a sequence between two PCR primers. Further, Dr. Goddard explains that the assay is extremely sensitive technique which leads to accurate determination of gene copy number. Dr. Goddard adds that the TaqMan PCR assay has been extensively and successfully used to characterize genes involved in cancer development and progression. For support, Dr. Goddard cites a number of references including a

publication by Pennica *et al.* in which Dr. Goddard is a co-author of the paper. Accordingly, a gene identified as being amplified at least 2-fold by the quantitative TaqMan PCR assay in a tumor sample relative to a normal sample is useful as a marker for the diagnosis of cancer, for monitoring cancer development and/or for measuring the efficacy of cancer therapy.

Further, Applicants have submitted Dr. Ashkenazi's Declaration to show that simultaneous testing of gene amplification and gene product over-expression enables more accurate tumor classification, even if the gene product (the protein) is not over expressed. Such experiments are carried out with the HER-2/neu protein in order to select patients for treatment with Herceptin monoclonal antibody therapy, as described in the Hanna paper. Thus the PRO1788 polypeptide has utility, in conducting such testing, regardless of whether or not the PRO1788 polypeptide is overexpressed.

Applicants have clearly shown that the gene encoding the PRO1788 polypeptide is amplified in at least eight primary colon tumors. Therefore, the PRO1788 gene, similar to the HER-2/neu gene disclosed in Hanna *et al.*, is a tumor associated gene. Furthermore, as discussed above, in the majority of amplified genes, the teachings in the art overwhelmingly show that gene amplification influences gene expression at the mRNA and protein levels. Therefore, one of skill in the art would reasonably expect in this instance, based on the amplification data for the PRO1788 gene, that the PRO1788 polypeptide is concomitantly overexpressed.

However, even if gene amplification does not result in overexpression of the gene product (*i.e.*, the protein) an analysis of the expression of the protein is useful in determining the course of treatment, as supported by the Ashkenazi Declaration. The Examiner asserts that "there is no evidence as to whether the gene products (such as the polypeptide) are over-expressed or not." (Page 4 of the instant Office Action). The Examiner appears to view the testing described in the Ashkenazi Declaration and the Hanna paper as experiments involving further characterization of the PRO1788 polypeptide itself. In fact, such testing is for the purpose of characterizing not the PRO1788 polypeptide, but the tumors in which the gene encoding PRO1788 is amplified. The PRO1788 polypeptide and the claimed antibodies which bind it are therefore useful in tumor categorization, the results of which become an important tool in the hands of a physician enabling the selection of a treatment modality that holds the most promise for the successful treatment of a patient

The Examiner asserts that the gene amplification data provided in the specification cannot provide utility for the claimed PRO1788 polypeptides because "gene amplification (i.e., as it relates to the instant specification) is not equivalent to gene expression (i.e., mRNA), which is not the same as polypeptide data (i.e., as claimed)" (Page 5 of the instant Office Action).

Applicants respectfully submit that the Orntoft *et al.,* Hyman *et al.,* and Pollack *et al.* references, as previously stated in the Applicants' response filed on January 16, 2005, collectively teach that in general, gene amplification increases mRNA expression. Applicants further submit that Dr. Polakis' Declaration was presented to support the position that there is a correlation between mRNA levels and polypeptide levels. Thus, taken together, all of the submitted evidence supports Applicants' position that gene amplification is more likely than not predictive of increased mRNA and polypeptide levels.

The Examiner asserts that "Orntoft *et al.* do not look at gene amplification, mRNA levels and polypeptide levels from a single gene at a time.... Orntoft *et al.* concentrated on regions of chromosomes with strong gains of chromosomal material containing clusters of genes ...this analysis was not done for PRO1788 in the instant specification. In other words, it is not clear whether or not PRO1788 is in a gene cluster in a region of a chromosome that is highly amplified. Therefore, the relevance, if any of Orntoft *et al.* is not clear." The Examiner further alleges, "Hyman *et al.* used the same CGH approach in their research. Less than half (44%) of highly amplified genes showed mRNA overexpression (abstract).... Therefore, Hyman *et al.* can not support the establishment of utility for the claimed polypeptides." The Examiner further alleges that "Pollack *et al.* also used CGH technology, concentrating on large chromosome regions showing high amplification (pg. 12965). Pollack *et al.* did not investigate polypeptide levels." The Examiner concludes that "Applicants' conclusion that these references support their contention that "[i]n a cast majority of amplified genes, the teachings of the art, as exemplified by Orntoft *et al.*, Hyman *et al.*, Pollack *et al.*...overwhelmingly show that gene amplification influences gene expression at the mRNA **and protein levels** [emphasis added]" is a clear mischaracterization of the teachings of Orntoft *et al.*, Hyman *et al.*, Pollack *et al.*" (See page 8 of the instant Office Action).

In Orntoft *et al.*, 1,800 genes that yielded an increase or decrease in mRNA expression in two invasive tumors compared to the two non-invasive papillomas were then mapped to chromosomal locations. The chromosomes had already been analyzed for amplification by

hybridizing tumor DNA to normal metaphase chromosomes (CGH). Orntoft *et al.* used CGH alterations as the independent variable and estimated the frequency of expression alterations of the 1,800 genes in the chromosomal areas. Orntoft *et al* found that in general (77% and 80% concordance) areas with a strong gain of chromosomal material contained a cluster of genes having increased mRNA expression (see page 40). Orntoft *et al.* state, "For both tumors TCC733 ($p<0.015$) and TCC827 ($p<0.00003$) a highly significant correlation was observed between the level of CGH ratio change (reflecting the DNA copy number) and alterations detected by the array based technology" (see page 41, column 1). Orntoft *et al.*, also studied the relation between altered mRNA and protein levels using 2D-PAGE analysis. Orntoft *et al.* state, "In general there was a highly significant correlation ($p<0.005$) between mRNA and protein alterations.... 26 well focused proteins whose genes had a known chromosomal location were detected in TCCs 733 and 335, and of these 19 correlated ($p<0.005$) with the mRNA changes detected using the arrays." (See page 42, column 2 to page 34, column 2). Accordingly, Orntoft *et al.* clearly support Applicants' position that proteins expressed by genes that are amplified in tumors are useful as cancer markers.

The Examiner indicates that Applicants have not indicated whether PRO1788 is in a gene cluster region of a chromosome. (See page 8 of the instant Office Action). Applicants fail to see how this is relevant to the analysis. Orntoft *et al.* did not limit their findings to only those regions of amplified gene clusters. Further, as discussed below, Hyman *et al.* and Pollack *et al.* did gene-by-gene analysis across all chromosomes.

Applicants respectfully submit that the Examiner has mischaracterized the methods used by Hyman *et al.* and Pollack *et al* in their analysis. These papers did not use traditional CGH analysis to identify amplified genes. In Hyman *et al.*, 13,824 cDNA clones were placed on glass slides in a microarray and genomic DNA from breast cancer cell lines and normal human WBCs were hybridized to the cDNA sequences. For expression analysis, RNA from tumor cell lines were hybridized on the same microarrays. The 13,824 arrayed cDNA clones were analyzed for gene expression and gene copy number in 14 breast cancer cell lines. Hyman *et al.* state, "The results illustrate a considerable influence of copy number on gene expression patterns." For example, Hyman *et al.* teach that "[u]p to 44% of the highly amplified transcripts (CGH ratio, >2.5) were overexpressed (*i.e.*, belonged to the global upper 7% of expression ratios) compared with only 6% for genes with normal copy number." (See page 6242, column 1). Further, Hyman

et al. state that "[t]he cDNA/CGH microarray technique enables the direct correlation of copy number and expression data on a gene-by-gene basis throughout the genome." (See page 6242, column 2). Therefore, the analysis performed by Hyman *et al.* was on a gene-by gene basis, and clearly shows that "it is more likely than not" that a gene which is amplified in tumor cells will have increased gene expression.

In Pollack *et al.*, DNA copy number alteration across 6,691 mapped human genes in 44 predominantly advanced primary breast tumors and 10 breast cancer cell lines was profiled. Pollack *et al.* further state, "Parallel microarray measurements of mRNA levels reveal the remarkable degree to which variation in gene copy number contributes to variation in gene expression in tumor cells." (See Abstract). "Genome-wide, of 117 high-level DNA amplifications (fluorescence ratios >4, and representing 91 different genes), 62% (representing 54 different genes; ...) are found associated with at least moderately elevated mRNA levels (mean-centered fluorescence ratios >2), and 42% (representing 36 different genes) are found associated with comparably highly elevated mRNA levels (mean-centered fluorescence ratios >4)." (See page 12966, column 1). Therefore, the analysis performed by Pollack *et al.* was also on a gene-by gene basis, and clearly shows that "it is more likely than not" that a gene which is amplified in tumor cells will have increased gene expression.

With regard to the correlation between mRNA expression and protein levels, Applicants previously submitted a Declaration by Dr. Polakis, principal investigator of the Tumor Antigen Project of Genentech, Inc., the assignee of the present application, to show that mRNA expression correlates well with protein levels, in general. As Dr. Polakis explains, the primary focus of the microarray project was to identify tumor cell markers useful as targets for both the diagnosis and treatment of cancer in humans. The scientists working on the project extensively rely on results of microarray experiments in their effort to identify such markers. As Dr. Polakis explains, using microarray analysis, Genentech scientists have identified approximately 200 gene transcripts (mRNAs) that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. To the date of the Declaration, they have generated antibodies that bind to about 30 of the tumor antigen proteins expressed from these differentially expressed gene transcripts and have used these antibodies to quantitatively determine the level of production of these tumor antigen proteins in both human cancer cells and corresponding normal cells. Having compared the levels of mRNA and protein in both the tumor and normal cells

analyzed, they found a very good correlation between mRNA and corresponding protein levels. Specifically, in approximately 80% of their observations they have found that increases in the level of a particular mRNA correlates with changes in the level of protein expressed from that mRNA. While the proper legal standard is to show that the existence of correlation between mRNA and polypeptide levels is more likely than not, the showing of approximately 80% correlation for the molecules tested according to the Polakis Declaration greatly exceeds this legal standard. Based on these experimental data and his vast scientific experience of more than 20 years, Dr. Polakis states that, for human genes, increased mRNA levels typically correlate with an increase in abundance of the encoded protein. He further confirms that "it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein."

The Examiner contends that the Polakis Declaration is insufficient to overcome the rejection of claims 38-35 and 38-40 since it is limited to a discussion of data regarding the correlation of mRNA levels and polypeptide levels and not gene amplification levels. The Examiner further alleges that only Dr. Polakis' conclusions are provided in the Declaration. Thus, the Examiner asserts that "no evidence is presented to support Dr. Polakis' statement that 'it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded polypeptide.'" (Page 5 of the instant Office Action).

Applicants respectfully submit that Dr. Polakis' Declaration is presented to support the position that there is a correlation between mRNA levels and polypeptide levels. Regarding the Examiner's rejection of the Polakis Declaration as lacking "evidence" Applicants emphasize that the opinions expressed in the Polakis Declaration, including the quoted statement, are all based on factual findings. Thus, Dr. Polakis explains that in the course of their research using microarray analysis, he and his co-workers identified approximately 200 gene transcripts that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. Subsequently, antibodies binding to about 30 of these tumor antigens were prepared, and mRNA and protein levels were compared. In approximately 80% of the cases, the researchers found that increases in the level of a particular mRNA correlated with changes in the level of protein expressed from that mRNA when human tumor cells are compared with their corresponding normal cells. Dr. Polakis' statement that "an increased level of mRNA in a tumor

cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell" is based on factual, experimental findings, clearly set forth in the Declaration. Accordingly, the Declaration is not merely conclusive, and the fact-based conclusions of Dr. Polakis would be considered reasonable and accurate by one skilled in the art.

The case law has clearly established that in considering affidavit evidence, the Examiner must consider all of the evidence of record anew.[18] "After evidence or argument is submitted by the applicant in response, patentability is determined on the totality of the record, by a preponderance of the evidence with due consideration to persuasiveness of argument" [19] Furthermore, the Federal Court of Appeals held in *In re Alton*, "[w]e are aware of no reason why opinion evidence relating to a fact issue should not be considered by an examiner"[20]. Applicants also respectfully draw the Examiner's attention to the Utility Examination Guidelines[21] which states that, "Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered." The statement in question from an expert in the field (the Polakis Declaration) states that "it is my considered scientific opinion that for human genes, an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell." Therefore, barring evidence to the contrary regarding the above statement in the Polakis Declaration, this rejection is improper under both the case law and the Utility guidelines.

The Examiner further asserts that the cited references by Haynes *et al.*, Pennica *et al.*, and Konopka *et al.* support the Examiner's position that "'more likely than not' no generalized correlation exists between gene (DNA) amplification and increased polypeptide levels." (Page 7 of the instant Office Action).

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[18] *In re Rinehart* 531 F.2d 1084, 189 USPQ 143 (C.C.P.A. 1976) and *In re Piasecki* 745 F.2d. 1015, 226 USPQ 881 (Fed. Cir. 1985).

.[19]. *In re Alton* 37 USPQ2d 1578, 1584 (Fed. Cir 1996) (quoting *In re Oetiker* 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992)).

[20] *In re Alton, supra.*

[21] Part IIB, 66 Fed. Reg. 1098 (2001).

As a preliminary matter, Applicants respectfully submit that it is not a legal requirement to establish a necessary correlation between an increase in the copy number of the mRNA and protein expression levels that would correlate to the disease state or that it is "imperative" to find evidence that protein levels can be accurately predicted. As discussed above, the evidentiary standard to be used throughout *ex parte* examination of a patent application is a preponderance of the totality of the evidence under consideration. Accordingly, the question is not whether a necessary or even "strong" correlation between an increase in copy number and protein expression levels exists, but whether it is more likely than not that a person of ordinary skill in the pertinent art would recognize such a positive correlation. Applicants respectfully submit that when the proper evidentiary standard is applied, a correlation must be acknowledged.

Applicants respectfully submit that, for the reasons previously set forth in the Applicants' response filed on February 2, 2005, Pennica *et al.* and Konopka *et al.* do not show a lack of correlation between gene (DNA) amplification and elevated mRNA levels. In particular, the combined teachings of Pennica and Konopka are not directed towards genes in general but to a single gene or genes within a family and thus, their teachings cannot support a general conclusion regarding correlation between gene amplification and mRNA levels.

The Examiner asserts that the Haynes *et al.* reference was cited as providing evidence that "protein levels cannot be accurately predicted from the level of corresponding mRNA transcript." Applicants respectfully point out that, on the contrary, Haynes teaches that "*there was a general trend* but no strong correlation between protein [expression] and transcript levels" (See page 1863, under Section 2.1, emphasis added). For example, in Figure 1, there is a positive correlation between mRNA and protein amongst *most* of the 80 yeast proteins studied, but the correlation is not linear, hence authors suggest that one cannot *accurately* predict protein levels from mRNA levels. In fact, very few data points deviated or scattered away from the expected normal or showed a lack of correlation between mRNA: protein levels. Thus, the Haynes data meets the "more likely than not standard" and shows that a positive correlation exists between mRNA and protein.

Accordingly, as stated above, since the standard is not absolute certainty, a *prima facie* showing of lack of utility has not been made in this instance and the burden to provide further evidence of utility has not shifted to Applicants.

The Examiner also cites Hu *et al.* to the effect that genes displaying a 5-fold change or less in mRNA expression in tumors compared to normal showed no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease. (Page 5 of the instant Office Action).

Applicants submit that in order to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Accordingly, contrary to the Examiner's assertion, Applicants respectfully submit that Hu *et al.* does not conclusively show that it is more likely than not that the gene amplification does not result in increased expression at the mRNA and polypeptide levels.

First, the title of Hu *et al.* is "Analysis of Genomic and Proteomic Data Using Advanced Literature Mining." As the title clearly suggests, the conclusion suggested by Hu *et al.* is merely based a statistical analysis of the information disclosed in the published literature. As Hu *et al.* states, "We have utilized a computational approach to literature mining to produce a comprehensive set of gene-disease relationships." In particular, Hu *et al.* relied on MedGene Database and the Medical Subject Heading (MeSH) files to analyze the gene-disease relationship. More specifically, Hu *et al.* "compared the MedGene breast cancer gene list to a gene expression data set generated from a micro-array analysis comparing breast cancer and normal breast tissue samples." (See page 408, right column).

Therefore, Applicants submit that the reference by Hu *et al.* only studies the statistical analysis of microarray data and not the gene amplification data. Hence, their findings would not be directly applicable to the gene amplification data. In addition, the Hu *et al.* reference does not show a lack of correlation between microarray data and the biological significance of cancer genes.

Further, the analysis by Hu *et al.* has certain statistical flaws. According to Hu *et al.*, "*different* statistical methods" were applied to "*estimate* the strength of gene-disease relationships and evaluated the results." (See page 406, left column, emphasis added). Using these different statistical methods, Hu *et al.* "[a]ssessed the relative strengths of gene-disease relationships based on the frequency of both co-citation and single citation." (See page 411, left column). It is well

known in the art that various statistical methods allow different variables to be manipulated to affect the outcome. For example, the authors admit, "Initial attempts to search the literature using" the list of genes, gene names, gene symbols, and frequently used synonyms, generated by the authors "revealed several sources of false positives and false negatives." (See page 406, right column). The authors further admit that the false positives caused by "duplicative and unrelated meanings for the term" were "difficult to manage." Therefore, in order to minimize such false positives, Hu *et al.* disclose that these terms "had to be eliminated entirely, thereby reducing the false positive rate but unavoidably under-representing some genes." *Id.* (emphasis added). Hence, Applicants respectfully submit that in order to minimize the false positives and negatives in their analysis, Hu *et al.* manipulated various aspects of the input data.

Applicants further submit that the statistical analysis by Hu *et al.* is not a reliable standard because the frequency of citation only reflects the current research interest of a molecule but not the true biological function of the molecule. Indeed, the authors acknowledge that "[r]elationship established by frequency of co-citation do not necessarily represent a true biological link." (See page 411, right column). It often happens in the scientific study that important molecules were overlooked by the scientific society for many years until the discovery of their true function. Therefore, Applicants submit that Hu *et al.* drew their conclusion based on a very unreliable standard and their research does not provide any meaningful information regarding the correlation between the microarray data and the biological significance.

Even assuming that Hu *et al.* provide evidence to support a true relationship, the conclusion in Hu *et al.* only applies to a specific type of breast tumor (estrogen receptor (ER)-positive breast tumor) and can not be generalized as a principle governing microarray study of breast cancer in general, l*et al*one the various other types of cancer genes in general. In fact, even Hu *et al.* admit that "[i]t is likely that this threshold will change depending on the disease as well as the experiment. Interestingly, the observed correlation was only found among ER-positive (breast) tumors not ER-negative tumors." (See page 412, left column). Therefore, based on these findings, the authors add, "This may reflect a bias in the literature to study the more prevalent type of tumor in the population. Furthermore, this emphasizes that caution must be taken when interpreting experiments that may contain subpopulations that behave very differently." *Id.* (emphasis added).

Accordingly, Applicants respectfully submit that the Examiner has not shown that a lack of correlation between microarray data and the biological significance of cancer genes.

The Patent Office has failed to meet its initial burden of proof that Applicant's claims of utility are not substantial or credible. The arguments presented by the Examiner in combination with the Pennica, Konopka, Haynes, and Hu papers do not provide sufficient reasons to doubt the statements by Applicants that PRO1788 has utility. As discussed above, the law does not require the existence of a "strong" or "linear" correlation between mRNA and protein levels. Nor does the law require that protein levels be "accurately" predicted. According to the authors themselves, the data in the above cited references confirm that there is a general trend between protein expression and transcript levels, which meets the "more likely than not standard" and shows that a positive correlation exists between mRNA and protein. Therefore, Applicants submit that the Examiner's reasoning is based on a misrepresentation of the scientific data presented in the above cited reference and application of an improper, heightened legal standard. In fact, contrary to what the Examiner contends, the art indicates that, if a gene is amplified in cancer, it is more likely than not that the encoded protein will be expressed at an elevated.level.

Taken together, although there are some examples in the scientific art that do not fit within the central dogma of molecular biology that there is a correlation between polypeptide and mRNA levels, these instances are exceptions rather than the rule. In the majority of amplified genes, the teachings in the art, as exemplified by Orntoft *et al.,* Hyman *et al.,* Pollack *et al.,* and the Polakis Declaration, overwhelmingly show that gene amplification influences gene expression at the mRNA and protein levels. Therefore, one of skill in the art would reasonably expect in this instance, based on the amplification data for the PRO1788 gene, that the PRO1788 polypeptide is concomitantly overexpressed. Thus, Applicants submit that the claimed PRO1788 polypeptides have utility in the diagnosis of cancer and based on such a utility, one of skill in the art would know exactly how to use the claimed polypeptides for diagnosis of cancer.

Accordingly, Applicants request the Examiner to reconsider and withdraw the rejection of Claims 28-35 and 38-40 under 35 U.S.C. §101 and §112, first paragraph.

III. Claim Rejections Under 35 U.S.C. § 112, First Paragraph (Written Description)

Claims 28-33 and 39-40 remain rejected under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as

to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The Examiner asserts that " a recitation related to DNA does not reasonably constitute a 'functional limitation' for the claimed polypeptides." The Examiner further asserts that Applicants have not described "a representative number of species that have 80-99% homology to SEQ ID NO:397, such that it is clear that they were in possession of a genus of polypeptides functionally similar to SEQ ID NO:397." (Pages 10-11 of the instant Office Action).

Applicants respectfully disagree and traverse the rejection. For the reasons discussed below, Applicants respectfully submit that Claims 28-35 and 38-40 satisfy the written description requirement under 35 U.S.C. §112, first paragraph.

The Legal Test for Written Description

The well-established test for sufficiency of support under the written description requirement of 35 U.S.C. §112, first paragraph, is "whether the disclosure of the application as originally filed reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter, rather than the presence or absence of literal support in the specification for the claim language."[22, 23] The adequacy of written description support is a factual issue and is to be determined on a case-by-case basis.[24] The factual determination in a written description analysis depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure.[25, 26]

In *Environmental Designs, Ltd. v. Union Oil Co.*[27], the Federal Circuit held, "Factors that may be considered in determining level of ordinary skill in the art include (1) the educational level of the inventor; (2) type of problems encountered in the art; (3) prior art solutions to those problems; (4) rapidity with which innovations are made; (5) sophistication of the technology; and

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[22] *In re Kaslow*, 707 F.2d 1366, 1374, 212 USPQ 1089, 1096 (Fed. Cir. 1983).

[23] *see also Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116 (Fed. Cir. 1991).

[24] *See, e.g., Vas-Cath*, 935 F.2d at 1563; 19 USPQ2d at 1116.

[25] *Union Oil v. Atlantic Richfield Co.*, 208 F.2d 989, 996 (Fed. Cir. 2000).

[26] *See also* M.P.E.P. §2163 II(A).

[27] 713 F.2d 693, 696, 218 USPQ 865, 868 (Fed. Cir. 1983), *cert. denied*, 464 U.S. 1043 (1984).

(6) educational level of active workers in the field." (Emphasis added).[28] Further, the "hypothetical 'person having ordinary skill in the art' to which the claimed subject matter pertains would, of necessity have the capability of understanding the scientific and engineering principles applicable to the pertinent art."[29, 30].

The Disclosure Provides Sufficient Written Description for the Claimed Invention

First, Applicants respectfully maintain the position that that Claims 28-35 and 38-40 satisfy the written description requirement under 35 U.S.C. §112, first paragraph, for the reasons previously set forth in Applicants' Response filed on January 18, 2005.

Applicants have amended Claims 28-32 to recite an isolated native sequence polypeptide. Applicants respectfully submit that the instant specification evidences the actual reduction to practice of the amino acid sequence of SEQ ID NO:397. TheExaminer has acknowledged that polypeptides comprising the sequence set forth in SEQ ID NO:397 meet the written description provision of 35 U.S.C. §112, first paragraph. (Page 7 of the Office Action mailed September 16, 2004). Thus, the genus of native sequence polypeptides with at least 80% sequence identity to SEQ ID NO:397, which possess the functional property of having a nucleic acid which is amplified in colon tumors would meet the requirement of 35 U.S.C. §112, first paragraph, as providing adequate written description.

Applicants have provided native PRO sequence SEQ ID NO:397. The present application also describes methods for identifying genes which are amplified in colon cancer.

Example 143 of the present application provides step-by-step guidelines and protocols for the gene amplification assay. By following the disclosure in the specification, one skilled in the art can easily test whether a gene encoding a native variant PRO1788 protein is amplified in lung and colon tumors. The specification further describes methods for the determination of percent identity between two amino acid sequences. (See page 302, line 4 to page 305, line 4). In fact, the specification teaches specific parameters to be associated with the term "percent identity" as applied to the present invention. Accordingly, one of skill in the art could identify whether the

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[28] *See also* M.P.E.P. §2141.03.

[29] *Ex parte Hiyamizu*, 10 USPQ2d 1393, 1394 (Bd. Pat. App. & Inter. 1988) (emphasis added).

[30] *See also* M.P.E.P. §2141.03.

variant PRO1788 native sequence falls within the parameters of the claimed invention. Once such an amino acid sequence was identified, the specifications sets forth methods for making the amino acid sequences (see page 354, line 30 to page 358, line 34) and methods of preparing the PRO polypeptides (see page 358, line 35 and onward).

Therefore, Applicants respectfully submit that one of skill in the art could readily test a nucleic acid sequence which encodes the variant polypeptide to determine whether it is amplified by the methods set forth in Example 143.

The Examiner asserts that " a recitation related to DNA does not reasonably constitute a 'functional limitation' for the claimed polypeptides." (Page 10 of the instant Office Action). Applicants respectfully disagree, and submit that a functional limitation is often used in association with an element, ingredient, or step of a process to define a particular capability or *purpose that is served by the recited element*, ingredient or step." (emphasis added) (see MPEP 2173.05(g)).

Gene expression is a process by which a gene's coded information is converted into RNA through transcription, or into proteins through both transcription and translation. Both transcription and translation are well-regulated and multi-step biological activities. As the overexpression of a gene in colon, lung or breast tumor cells correlates with a higher level of activity of transcription and/or translation of this gene, overexpression of the claimed nucleic acid in colon, lung or breast tumor cells is a functional limitation which indicates the activity of the claimed polypeptide.

Additionally, Applicants are claiming native sequence polypeptide sequences. It is understood that many polypeptides and especially tumor antigens are known to have different isoforms or variants. Applicants have provided the sequence of native PRO sequence SEQ ID NO:397. As indicated above, given the specification, one skilled in the art could readily identify native variants or isoforms of this PRO1788 sequence. It would be a simple matter for one skilled in the art to test the nucleic acids to see if they are over expressed in colon tumors using the methods of Example 143.

Accordingly, the specification provides adequate written description for native sequence polypeptides having at least 80% identity to SEQ ID NO:397 wherein the nucleic acid encoding the polypeptide is amplified in colon tumors. For the above reasons, Applicants respectfully request that the rejection be withdrawn and the claims be allowed.

CONCLUSION

In conclusion, the present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited. Should there be any further issues outstanding, the Examiner is invited to contact the undersigned attorney at the telephone number shown below.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (referencing Attorney's Docket No. **39780-2830 P1C42**).

Respectfully submitted,

Date: July 8, 2005

By: _____
Barrie D. Greene (Reg. No. 46,740)

HELLER EHRMAN LLP
275 Middlefield Road
Menlo Park, California 94025-3506
Telephone: (650) 324-7000
Facsimile: (650) 324-0638

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